inhibits plasmin activity (see page 7, lines 10-13) which results in inhibition of growth and metastatic spread of malignant tumors (see page 6, lines 20-31).

The specification has also been amended by the foregoing amendments in order to insert proper section headings. Support for the text under "Summary of the Invention" can be found, at the very least, on page 1 of the specification as filed. Support for the description of Figure 1 can be found on page 4, lines 24-30, of the specification as filed. Support for the description of Figure 2 can be found on 7, lines 14-24, of the specification as filed. No new matter has been added by the present amendment.

Objection to the Specification

The Examiner has objected to the specification for purportedly not conforming to the preferred arrangement of a patent application. By the present amendment, applicants have amended the specification to provide the proper section headings. In light of this amendment, applicants respectfully request withdrawal of this objection to the specification.

Rejection of Claim 11 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claim 11 under 35 U.S.C. § 112, first paragraph, because the specification purportedly is not enabling for the prevention of tumors and neoplasms. Applicants respectfully traverse this rejection.

Claims 10 and 11 have been amended to clarify that the invention relates to the disease state of cancer in which growth of tumors and neoplasms occurs and in which metastasis occurs. As can be seen on page 7 of the specification boswellic acid inhibits

plasmin activity. As described on page 6 of the specification, plasmin is released from tumor cells and catalyses the hydrolysis of peptide bounds which leads to the degradation of a number of proteins and peptides. The increased activity of plasmin is held responsible for the invasive growth and metastatic spread of malignant tumors, which is accompanied by the destruction of endogenous functional tissue. The present invention claims the prevention of growth and metastatic spread of malignant tumors, not the prevention of cancer itself (as the Examiner appears to assert). Clearly there is support for preventing growth and metastatic spread of malignant tumors (see, for example, pages 6 and 7 of the specification as filed). In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Rejection of Claim 16 Under 35 U.S.C. § 112, Second Paragraph

Claim 16 has been rejected to under 35 U.S.C. § 112, second paragraph, for purportedly being indefinite for failing to particularly point out and distinctly claimed the subject matter which applicants regard as the invention. Specifically, the Examiner purports that the terms "chemically pure" and "substance" are indefinite. Applicants respectfully traverse this rejection.

One of skill in the art, from reading the specification, would clearly know what is meant by "chemically pure medicinal or plant substance". For example, at page 13, lines 12-14, applicants disclose that the preparations used for the method can also contain one or more pharmaceutically acceptable carriers or diluents. One of skill in the art would also know how to chemically purify any medicaments or plant substances used in preparations

used for the method of the invention. Furthermore, one of skill in the art would know, by reading the specification, what is meant by "plant substance". For example, at page 12, lines 9-21, of the specification, applicants describe a preferred plant preparation, which is an extract of *Boswellia serrata*, and comprises, amongst other plant substances, boswellic acid. Thus, one of ordinary skill in the art would clearly be aware of the scope of the invention.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 10-16 Under 35 U.S.C. § 103(a)

Claims 10-16 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Taneja et al. (U.S. Patent No. 5,629,351), in view of Lee et al. (U.S. Patent No. 5,064,823) and Patwardhan (U.S. Patent No. 5,494,668). Specifically, the Examiner purports that Taneja et al. teaches the anti-inflammatory, anti-arthritic and anti-ulcerogenic activity of boswellic acids. Furthermore, according to the Examiner, Lee et al. teach treating various cancers by administering various pentacyclic triterpenoid compounds, such as boswellic acid. Finally, the Examiner purports that Patwardhan teach treating rheumatoid arthritis and osteoarthritis by administering plant extracts which include boswellic acid. This rejection is respectfully traversed.

"Inflammatory diseases" is not a term characterizing a group of defined diseases, but describes the formation of historically defined symptoms of inflammation (i.e., redness, heat, edema, pain and loss of function) which can be promoted by a multifold of totally

different diseases and pathological causes. The different protective reactions of the organism as a reaction against harmful and noxious agents, such as acids or bases, heat, virus, bacteria, and fungi, can lead to morphological changes. These changes lead to the symptoms of, for example, redness, heat, edema, pain and loss of function. These symptoms are caused by a vast variety of pathophysiological events in the body. Different cells and mediator systems and messenger substances are involved in these inflammatory processes, which can be acute, chronic, destructive or recurring. The organs involved are also differing and consequently also the pharmacotherapy varies widely.

Hydrolytic enzymes, according to the present invention human leucocytic elastase (HLE) and plasmin, are particularly important for two different diseases. First, there are certain chronic inflammatory diseases in the course of which there is an infiltration by neutrophiles. These neutrphiles are activated by other mediators and release large amounts of HLE. HLE leads to terminal damage. Human diseases which are associated with an increased release of HLE are pulmonary emphysema, acute respiratory distress syndrom, shock lung, cystic fibrosis, chronic bronchitis, glomerulonephritis and rheumatoid arthritis (see page 2 of the application as filed). Boswellic acids can prevent liver damage by blocking the enzyme HLE (see Safayhi et al. "Inhibition by Boswellic Acids of Human Leukocyte Elastase," *J. Pharm. Exp. Therap. 281(1)*:460-463 (1997), a copy of which is attached as Exhibit A). This inhibition of an increased free HLE activity is not a therapy of the inflammatory processes, but a prevention of the HLE mediated damage to structures and cells of the body in the course of inflammatory diseases.

Second, as mentioned previously, plasmin is released from tumor cells and catalyses the hydrolysis of peptide bonds, which leads to the degradation of a number of proteins and peptides. The increased activity of plasmin is held responsible for the invasive growth and metastatic spread of malignant tumors, which is accompanied by the destruction of endogenous functional tissue (see page 6 of the specification as filed).

Taneji et al. discloses the anti-inflammatory activity of a novel fraction comprising a mixture of boswellic acid. The authors of Taneji et al. tested this extract and determined its anti-inflammatory activity on the basis of the paw edema model in rats/mice. This model, however, is a model for the activity of the cyclooxygenase/their products (prostaglandins), which lead to an increased vascular permeability and thus to swelling of the paw. This is demonstrated by the fact that in this system generally inhibitors of the cyclooxygenase (PGH synthase inhibitors, inhibitors of the prostaglandine biosynthesis, non-steroidal anti-inflammatory drugs) are used as positive controls. In this connection, reference is made to Singh et al., "Pharmacology of an extract of salai guggal ex-*Boswellia serrata*, a new non-steroidal anti-inflammatory agent," *Agents and Actions 18(3/4)*:407-412 (1986) (a copy of which is attached as Exhibit B), in which the cyclooxygenase inhibitor phenylbutazone was used as an effective comparative substance. Cyclooxygenase inhibitors (NSAIDs) show only a minor anti-inflammatory effect with many diseases, basically the supression of the symptom of pain. For the indications claimed in the present invention, the use of NSAIDs is absolutely contraindicated.

As mentioned above, the present invention involves the inhibition of human leucocytic elastase activity. This inhibition of an increased free HLE activity is not a therapy of the inflammatory processes, but a prevention of the HLE mediated damage to structures and cells of the body in the course of inflammatory diseases. The authors of Taneji et al. do not teach the treatment of anti-inflammatory diseases caused by an influx of neutrophiles (which then release HLE). Furthermore, the authors of Taneji et al. do not teach or suggest that boswellic acid can be used to prevent HLE mediated damage to the structures and cells of the body in the course of inflammatory diseases. Therefore, the authors of Taneji et al. do not teach or suggest the present invention.

Patwardhan teaches treating degenerative musculoskeletal diseases, such as rheumatoid arthritis and osteoarthritis, by providing extracts from plants, including *Boswellia serrata* (which contains various forms of boswellic acid). The only reference in Patwardhan to data regarding boswellic acids effect on inflammation occurs in column 6, third paragraph, of the patent. Patwardhan states "[b]eta boswellic acid has significant anti-inflammatory activity in acute inflammation models in animals using carageenan induced paw edema and also in chronic rheumatoid artiritis . . . [i]t reduces triidothyronine levels in acute and chronic inflammation. In chronic conditions the acid increases thyroxine levels. It reduces both the volume and leucocyte population in pleural exudate."

As mentioned above, the present invention involves the inhibition of human leucocytic elastase activity. This inhibition of an increased free HLE activity is not a therapy of the inflammatory processes, but a prevention of the HLE mediated damage to

structures and cells of the body in the course of inflammatory diseases. Patwardhan does not teach the treatment of anti-inflammatory diseases caused by an influx of neutrophiles (which then release HLE). Furthermore, the Patwardhan does not teach or suggest that boswellic acid can be used to prevent HLE mediated damage to the structures and cells of the body in the course of inflammatory diseases. Therefore, Patwardhan does not teach or suggest the present invention.

Lee et al. teach that β-boswellic acid has an inhibitory effect on topoisomerase I and topoisomerase II, and thus can be used to treat various cancers. Topoisomerase I cleaves and reseals a single strand of DNA, and thus functions primarily to allow for transcription. Topoisomerase II is necessary for replication of DNA, and it allows for the creation of a double-strand break in the DNA helix, crossing over of a second DNA segment at the cleavage site (i.e. rotation of the two strands), and resealing of the helix. In these ways, topoisomerase I and II work to promote the unregulated growth of cancerous cells.

In contrast, the present invention relates to the inactivation of plasmin. Plasminogen (the precursor to plasmin) is released from cancerous cells and by proteolytic activation is transformed into plasmin. This enzyme is required to degrade the basement membrane and extracellular matrix and allow for the escape of the tumor cell into the interstitial space (metastasis). Furthermore, plasmin activates growth factors which can stimulate the reproduction of tumors (see page 6 of the specification as filed).

Lee et al. does not teach or suggest using boswellic acid to inhibit plasmin, thereby preventing reproduction of tumors and metastasis of tumors. Thus, Lee et al. does not teach or suggest the present invention.

In conclusion, none of the patents cited by the Examiner teach a method of preventing and/or combatting diseases which are caused by, or can be treated by the inhibition of, leucocytic elastase or plasmin activity, using boswellic acid. Therefore, none of these patents, either taken alone or together, teach or suggest the present invention. In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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